Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Overview of Clinical Outcome and Therapeutic Effectiveness of Favipiravir in Patients with COVID-19 Admitted to Intensive Care Unit, Riyadh, Saudi Arabia

Abbas Al Mutair, Jinan Shamou, Saad Alhumaid, Laila Layqah, Gasmelseed Y. Ahmad, Koritala Thoyaja, Mohammed Al Mohaini, Sana Almahmoud, Mazin Barry, Amjad Khan, Kuldeep Dhama, Lamiaa Hamad Al-Jamea, Alxeander Woodman, Ali A. Rabaan

PII: S1876-0341(22)00025-9

DOI: https://doi.org/10.1016/j.jiph.2022.01.013

Reference: JIPH1801

To appear in: *Journal of Infection and Public Health*

Received date: 4 October 2021
Revised date: 30 December 2021
Accepted date: 18 January 2022

Please cite this article as: Abbas Al Mutair, Jinan Shamou, Saad Alhumaid, Laila Layqah, Gasmelseed Y. Ahmad, Koritala Thoyaja, Mohammed Al Mohaini, Sana Almahmoud, Mazin Barry, Amjad Khan, Kuldeep Dhama, Lamiaa Hamad Al-Jamea, Alxeander Woodman and Ali A. Rabaan, Overview of Clinical Outcome and Therapeutic Effectiveness of Favipiravir in Patients with COVID-19 Admitted to Intensive Care Unit, Riyadh, Saudi Arabia, *Journal of Infection and Public Health,* (2021) doi:https://doi.org/10.1016/j.jiph.2022.01.013

Title: Overview of Clinical Outcome and Therapeutic Effectiveness of Favipiravir in Patients with COVID-19 Admitted to Intensive Care Unit, Riyadh, Saudi Arabia

Authors:
Abbas Al Mutair[1, 2, 3]
Jinan Shamou[4]
Saad Alhumaid[5]
Laila Layqah[6]
Gasmelseed Y. Ahmad[1]
Koritala Thoyaja[7]
Mohammed Al Mohaini[8,9]
Sana Almahmoud[10]
Mazin Barry[11]
Amjad Khan[12]
Kuldeep Dhama[13]
Lamiaa Hamad Al-Jamea[14]
Alxeander Woodman[14]
Ali A. Rabaan[15]

Author Affiliations:

1. Research Center Director, Almoosa Specialist Hospital, Alhassa, Saudi Arabia,
2. School of Nursing, University of Wollongong, Wollongong, Australia.
3. Princess Norah Bint Abdulrhamn University, Riyadh, Saudi Arabia
4. Department of Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia
5. Administration of Pharmaceutical Care, Al-Ahsa Health Cluster, Ministry of Health, Al-Ahsa, Saudi Arabia.
6. Research Office, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.
7. Department of Internal Medicine, Mayo Clinic Health System, Mankato, MN, USA.
8. Basic Sciences Department, College of Applied Medical Sciences, King Saud Bin Abdulaziz University for Health Sciences, Al-ahsa, Saudi Arabia.
9. King Abdullah International Medical Research Center, Al-ahsa, Saudi Arabia.
10. Department of Administration, College of Nursing, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
11. Division of Infectious Diseases, College of Medicine, King Saud University, Riyadh, Saudi Arabia
12. Department of Public Health/Nutrition, The University of Haripur, Pakistan
13. Division of Pathology, ICAR-Indian Veterinary, Bareilly, Uttar Pradesh, India
14. Vice Deanship of Postgraduate studies and Research, Prince Sultan Military College of Health Sciences, Dhahran Saudi Arabia

15. Molecular Diagnostics Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia

*** Corresponding author address:**
Dr Abbas Al Mutair
Email: abbas.almutair@almoosahospital.com

Author contributions:
AA- conception, proposal development, ethical approval, data recruitment, formal analysis and manuscript preparation.
JS- proposal development
SA- manuscript preparation
LL- manuscript refinement
GA- formal analysis
KT- manuscript refinement
MA- data recruitment
SA- manuscript preparation
MB- formal analysis
AK- manuscript refinement
KD- manuscript refinement
LA- manuscript refinement
AW- manuscript refinement
AR- manuscript preparation

Abstract:

Background: Prior to the availability of the current COVID-19 vaccine, the need to control the pandemic worldwide was focused on management of the disease using previously approved antivirals, including Favipiravir which inhibits viral replication through the RNA dependent RNA polymerase enzyme. Favipiravir's efficacy against different viral infections has made it a potential treatment for COVID-19. We are aiming in this study to assess the therapeutic efficacy and safety of Favipiravir in treating critically ill patients admitted with COVID-19 to Intensive Care Units (ICUs).

Methods: This is a retrospective cohort study was conducted in five tertiary hospitals in Riyadh, Kingdom of Saudi Arabia (KSA). The studied sample was randomized from a huge pool of data collected primarily for critically ill COVID-19 patients admitted to (ICUs) during the period between April 2020 to March 2021. Two groups of patients matched 1: 1 for age and body mass index (BMI) was enrolled in the study; one group received Favipiravir and another comparison group received other antimicrobial medications, not including Favipiravir.

Results: A total data of 538 COVID-19 patients were analyzed, 269 (50.%) received Favipiravir and 269 (50%) the control group received different treatments. More than two-thirds 201 (74.7%) were Saudi citizens, the majority 177 (65.8%) were males and the mean age and (BMI) were; (57.23 ± 15.16) years and (31.61±7.33) kg/m2 respectively. The most frequent symptoms of presentation were shortness of breath (SOB), fever, and cough, and the most frequent comorbidity was diabetes mellitus, hypertension, and ischemic heart disease.

In the supplemental therapy**,** corticosteroid, tocilizumab and chloroquine were statistically significant ($P = 0.001$) when combined in the FVP group more than in the comparison group. Severe acute respiratory distress syndrome (ARDS) was more frequent among Favipiravir group, while the overall mortality rate among the Favipiravir group was not statistically significant (p-value 0.4).

Conclusion:

According to the study's results revealing FVP is not superior to other antivirals, patients who received Favipiravir presented with more severe symptoms, more comorbidities, more complications, and is not effective in controlling the cytokine storm which negatively impact the efficacy of Favipiravir.

FVP therapy had no influence on ICU and hospital length of stay in comparison with the control group as well as in the overall mortality rate among the FVP group was not statistically significant. further research is needed to understand how FVP

along with other treatments can improve the length of stay among COVID-19 patients admitted to the ICU.

Keywords: COVID-19, Favipiravir, efficacy and safety, critically ill, ICU, Saudi Arabia.

Background

Since the end of 2019, a new type of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) disease, named coronavirus disease 2019 (COVID-19), has spread all over the world and ever since has been designated as a pandemic that originated in Wuhan, China [1, 2]. The World Health Organization (WHO) has declared that the coronavirus outbreak has become a global health concern[3].According to the WHO, the disease has affected over 220 million individuals worldwide and killed 4.5 million of them[4]. Although Covid-19 has been around for a while, there is so little we know about its origins and the way our immune system reacts to it [5].Understanding the clinical characteristics of COVID-19 assist in, identifying high-risk individuals, mapping the disease and directing future management[6] as we are learning to live with this disease, there is a need to discover new therapies or come up with efficient treatment strategies to counteract it. In addition to fever and chills, COVID-19 symptoms usually involve malaise, sore throat, dyspnea, cough, myalgia, and diarrhea which can be mistaken as traditional flu symptoms. However, these mild symptoms can quickly progress to severe respiratory distress leading to COVID associated acute respiratory distress syndrome (CARDS), which in turn can lead to death due to multi-organ failure[7].The severity of the disease differs amongst groups based on demographic characteristics, comorbidities, and immune system responses[8-10].

Several studies have found that variations in white blood cell count in COVID-19 individuals, such as lymphopenia, leukocytosis and leukopenia, are associated with the severity of the disease[9].

As a result of the unknown nature of the disease and lack of specialized medications, patients received a variety of potential treatments to learn if they are effective against the disease [11].Corticosteroids especially are highly effective in reducing inflammation and thereby reduce the progression of the disease [12]. Dexamethasone in particular has been proven to reduce mortality especially in patients undergoing invasive mechanical ventilation [13].

Clinical trials have been conducted on various anti-infective; some have been found to be effective, such as hydroxychloroquine[14], while others are still being examined. The goal of the clinical studies on antimalarial medication usage in Covid-19 was to show that hydroxychloroquine and chloroquine are efficacious in pre-exposure and post-exposure prevention and therapy[15].

It was found in meta-analysis study, Hydroxychloroquine alone was not effective for the treatment of COVID-19 patients and the combination of hydroxychloroquine with azithromycin significantly increased mortality [16]

The use of antiviral agents was explored based on the efficacy of Remdesivir on the COVID virus in the in-vitro studies on human lung primary cells and Vero E6 cells [17, 18]. Favorable in-vitro studies and clinical trials led to FDA's EUA approval for Remdesivir on May 1, 2020[19, 20]. It was found that antivirals are especially active in the early stages of disease pathogenesis owing to their ability to inhibit active viral replication. Their effectiveness is however limited in later stages of disease progression where a pro-inflammatory process overtakes necessitating the need for immunomodulatory drugs [21].

lopinavir (LPV), is a potent human immunodeficiency virus type 1 (HIV-1) protease inhibitor, that inhibits SARS-CoV in humans [22]. It is often used in combination with ritonavir (RTV) which increases the plasma half-life of LPV by inhibiting the Cytochrome P450 [23]. Lopinavir/ritonavir combination was shown anti -SARS-CoV-2 activity in patients and in vitro by inhibiting the protease in Vero E6 cells[22] Favipiravir(FVP)is an antiviral agent (Avigan)® or (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) that was safe and effective against a wide range of types and subtypes of virus infection like influenza and Ebola[24, 25]. FVP directly and selectively blocks the replication of flavi-RNA, alpha-RNA, filo-RNA, bunya-RNA, arena-RNA, noro-RNA, and other RNA viruses [26, 27]. [28,29]. In cells, FVP is transformed to an active phosphoribosylated form (favipiravir-ribofuranosyl-5'-triphosphateRTP), which is recognized as a substrate by viral RNA polymerase and inhibits RNA polymerase activity [25, 28], which might theoretically make it effective against SARS.-CoV-2 Early clinical experience with FVP in two trials showed favorable therapeutic responses in terms of viral clearance in adult inpatients infected with COVID-19[27, 30].

In the Arabian Peninsula, Saudi Arabia is the largest county has a well-developed health-care system that is available free to all citizens. In 2019, There are 494 hospitals in the health-care system, with 22.5 beds / 10,000 people and 113 000 physicians in the country[31, 32].

The Ministry of Health developed recommendations for health facilities, case treatment, epidemiological surveillance, and all slices of society. In addition, the Saudi Center for Disease Control issued an infection prevention and control guidebook to assist and guide all sectors throughout the COVID-19 pandemic[33] . The Ministry of Health's national response document, which is available online, has specifics on these instructions[31].

During the pandemic period in Saudi Arabia, Risk assessment, contingency planning, training and other educational initiatives are part of Preparedness. As well as the majority of emergency medical services (EMS) requests were received through a telephone call before and during the pandemic[34, 35].

Herein, we present a retrospective analysis of the clinical outcomes, assess the therapeutic efficacy and safety of FVP in treating critically ill patients with COVID-19 admitted to Intensive Care Units (ICUs), and finally compare with those who haven't received FVP treatment.

Design:

It is a retrospective cohort multicenter study, conducted in Riyadh hospitals to examine the overall survival outcome and hospital stay as the main predictors for the efficacy of FVP administered in critically ill COVID-19 patients admitted to ICUs between 1st April 2020 and 31st March 2021. The source of our data was a huge pool of data collected primarily from all the tertiary hospitals in Riyadh through the Research Electronic Data Capture (REDCap) registry. The data covered comprehensive information on; socio-demographic profile characteristics of the patients admitted to the ICU with COVID-19 infection, laboratory parameters, therapeutic interventions, invasive and non-invasive mechanical ventilation settings and modes, complications, and patients' outcomes in terms of overall survival and length of stay in the ICU and hospital. All patients (269) who received FVP were extracted consecutively. A control group with the same number was randomly selected in a 1:1 match for age and BMI. An ethical clearance to conduct the study was obtained from Institutional Review Board "REDACTED".

Since it is a retrospective study, the data was identified for publication purpose and no consent was required. The study has adhered to the ethical guidelines of the Declaration of Helsinki and good clinical practice through all stages of the study design.

Statistical analysis:

We applied the Statistical Package for Social Sciences (SPSS, version 25) as standard statistical procedure for the analysis. The collected data was first validated for accuracy and completeness before any statistical analysis was conducted on it. We have performed both descriptive and inferential statistical tests on these two groups of people to analyze our results further. In the descriptive analysis, the socio-demographic and clinical variables were analyzed and reported as frequencies and means ± standard deviation (SD). In inferential statistics, we have applied the chi-square test, t-test, survival analysis Kaplan Meier test, and binary logistics tests. Total number of patients who received FVP were made categorical (yes/ no) variables. A binary logistic regression was used to evaluate whether there is a significant difference in overall survival between these two groups of patients; patients who received FVP versus the group of patients treated with other medications. In this model, treatment with FVP was the dependent variable; survival status, length of hospital stays, and acute respiratory distress syndrome (ARDS) were the main independent categorical variables. Differences between treatment groups were considered statistically significant when the two-sided p-value was ≤ 0.05.

Results:

Data on 538 COVID-19 patients were analyzed using IBM-SPSS Version 25, half of them, 269 (50.0%) received FVP and the second half control group received

other different treatments. More than two-thirds 201 (74.7%) were Saudi citizens, the majority 177 (65.8%) were males and the mean age and (BMI) were; (57.23 ± 15.16) years and (31.61 ± 7.33) kg/m^2 respectively. Out of the 538 patients, 69 (12.8%) were smokers, as shown in Table I. Shortness of breath (SOB), fever, and cough were the most common presenting symptoms, while diabetes and hypertension were the most common co-existing morbidities as shown in table II.

Table IIIA represents the laboratory findings of the patients on ICU admission. Inflammatory markers D-dimer and C-reactive protein (CRP) were significantly lower in the FVP group (2.97 ± 5.70 vs. 5.21 ± 9.59, *P*=0.011) compared with the control group (106.03 ± 85.58 vs. 170.55 ± 282.69, *P*= 0.016).

In the supplemental therapy**,** corticosteroid, tocilizumab and chloroquine were applied combined in the FVP group more than in the comparison group (84% vs. 57%, 56%vs.19 %, 7% vs. 25%) respectively, table III B. The difference was statistically significant (*P* = 0.001). Severe acute respiratory distress syndrome (ARDS) was more frequent among the FVP group. However, the overall mortality rate among the FVP group was lower [119 (44.2%) vs. 128 (47.6%)], the difference was not significant (P-*value 0.4*), table IV.

The Kaplan–Meier survival curves for ICU- length of stay for both kinds of therapy were presented in Fig.1.

The median time of ICU LOS for the patients treated with FVP was estimated to be 12.5 days (IQR: 14), which was significantly longer than the time for patients in the other arm, which was 9 days (IQR: 9) (*P* < 0.001).

Discussion

FVP is an antiviral drug that has been used to treat COVID-19 infections in several countries throughout the world. This retrospective study described the clinical outcome and therapeutic effectiveness of FVP between hospitalized patients with COVID-19 who received antiviral treatment and those without it in Saudi Arabia. Out of 538 patients included in this study, 70% were male, 60 % were from Saudi Arabia and 13% were smokers, which is in accordance with the previous study where the majority of admitted ICU patients with COVID-19 were males (87.2%) and the most common symptoms were cough (96%) and shortness of breath (90%)[36]. The mean BMI for patients in our study in both groups was closer to 30kg/m^2 which correspond with the data presented in other studies reported in New York [37,38].Obesity is associated with poor outcomes in COVID-19 patients [39]. Since the patients in our study were not obese, it might not have influenced the outcomes on the patients on FVP and the control group. Our data also showed that there was no significant difference in the history of smoking age, and body mass index (BMI) between the two groups that is consistent with the result of the study conducted in Wuhan, China [40].

According to the medical records of our data, common symptoms of the patients with severe pneumonia COVID-19 were shortness of breath (86%), fever (67%) and dry cough (60%), but the difference was not statistically significant except for cough. The results on fever and shortness of breath are in line with the study conducted by (Wang et al) [40-42]. The improvement in the cough symptoms is in tune with another clinical study where FVP did not show any significant improvement in the patient's clinical condition but reduced the latency period for relief from cough symptoms[43].However, in the clinical study, the patients' febrile

condition improved but it didn't show any improvement in our FVP group's febrile condition.

Most of the poor prognostic indicators in COVID-19 hospitalized patients happen to be the presence of comorbidities and old age [42, 44, 45] .A retrospective study from Saudi Arabia in 352 hospitalized patients with COVID-19 showed that the most usual comorbidities were hypertension (51.1%) and diabetes mellitus (27.6%)[36]. In our study, the majority of the comorbidities were diabetes mellitus (66.5%), hypertension (56%), and ischemic heart disease (15%).

Due to the SARS-CoV-2 infection, the host exhibits an exaggerated immune response which is often identified by lymphopenia and cytokine storm[46, 47] . Studies have shown that Covid-19 patients have higher levels of cytokines which are linked to pulmonary inflammation, lung and multi-organ failure, often leading to death [47, 48]. The cytokine storm can be predicted by some laboratory values including lymphocyte count, CRP, D-dimer, and ferritin levels. The association between D-dimer and C-reactive protein is well established in COVID–19 patients [49]. Moreover, Vidali et al reported in a systematic review the correlation between the degree of elevation of D-dimer, the severity of disease, rate of complications, and prognosis of COVID-19 infection [50].

Early literature reported by WU *et al*. that D-dimer values in ARDS patients were significantly higher compared with non-ARDS patients (difference between the two groups 0.52 $\mu g \cdot mL^{-1}$, 95% CI 0.21–0.94 $\mu g \cdot mL^{-1}$; $p < 0.001$)[51]. Our findings showed that D-dimer values in COVID – 19 patients receiving FVP therapy (2.97 ± 5.70) was lower than the other group (5.21 ± 9.59); *P=0.011*.

The inflammatory response and cytokine storms caused by SARS-CoV-2 in the blood vessels lead to an increased level of CRP[52].This is in accordance with previous studies, which showed that the CRP level was positively correlated with the pneumonia severity[53].Our data showed CRP values in COVID – 19 patients in the FVP therapy arm (106.03 ± 85.58) is much less than the control arm without FVP treatment (170.55 ± 282.69); P=0.016. However, a study by Mortaz et al[54], on the effect of antiviral therapy (FVP or Kaletra) for 7 days on COVID-19 infected individuals showed a significant elevation in serum levels of IL-8 in non-ICU patients and TNFα, IL-1β, and IL-6 in ICU patients. TNFα, IL-1β, and IL-6 are some of the main factors that contribute to the cytokine storm[55]. Thus, FVP is not effective in controlling the cytokine storm.

In our observation, it was seen that the FVP therapy had no influence on ICU and hospital length of stay in comparison with the control group who received other treatments. Severe acute respiratory distress syndrome (ARDS) was more frequent among the FVP group (28% versus 26%) probably due to its inability in controlling the cytokine storm. Hospital length of stay was higher in the FVP group compare with others (24.98 ± 20.76 vs. 18.29 ± 19.14) that is consistent with the study conducted in Iran where the length of hospital stay was analogous in the two therapies (FVP, and Lopinavir), respectively 7 and 6 days[56]

The median time of ICU LOS for the patients treated with FVP was estimated to be 12.5 days (IQR: 14), which was significantly longer than the time for patients in the other arm, which was 9 days (IQR: 9) ($P < 0.001$). In line with the results seen in another controlled study where a group of 35 patients treated with FPV was compared with 45 patients who had received LPV/RTV. The median time of viral clearance for the patients treated with FPV was estimated to be 4 days (IQR: 2.5–

9), which was significantly shorter than the time for patients in the control arm, which was 11 d (IQR: 8–13) ($P < 0.001$) [22].

However, the overall mortality rate among the FVP group was lower [119 (44.2%) vs. 128 (47.6%)], the difference was not significant (*P-value= 0.4*), in contrast to the previous report, Kocayigit et al. a high mortality of 66.2% in patients with severe COVID-19 infections who received FVP versus 54.3%in the comparator drug[57] Khamisa et al. reported in another study, where the use of hydroxychloroquine was compared to FVP plus inhaled interferon beta-1b in patients with moderate to severe COVID-19 infection, FVP therapy were reported to have no significant effect in regards to overall mortality (11.4% vs 13.3%; p = 0.778) and ICU admission (18.2%vs 17.8%; p = 0.960)[58].The data from the study by Mortaz et al[54] suggests that treating COVID-19 patients with antiviral therapy can improve the clinical features of the lungs which were determined by blood markers (CRP, LDH, ESR, and CPK) and CT scans. However, this effect was not seen on the cytokine levels in the blood as their levels were increased significantly. Thus, it looks like the antivirals had no inhibitory effect on the upregulation of cytokines, and therefore even though the mortality rate is low, the antivirals could not prevent the development of the cytokine storm.

The negative results from this study regarding the effectiveness of FVP in COVID-19 pneumonia may be attributed to the pathogenicity mechanism of the coronavirus. COVID associated acute respiratory distress syndrome (CARDS) has three phases: an early infection phase with mild and non-specific symptoms, a pulmonary involvement phase with or without hypoxia, and a late phase which include the rise in inflammatory mediators known as a "cytokine storm" that leads to ARDS, which is associated with a high mortality rate. This was partly due to

delay in starting FVP therapy in the course of illness of these patients; this may have contributed to the lack of a meaningful favorable clinical benefit of FVP. Nonetheless, this result is not unique to our study, but was reported in other multiple studies; Chen et al[59] and Shrestha et al [60] said that FVP therapy showed no effect on viral clearance or the need for assisted ventilation when compared to other therapies or the standard of care.

Conclusion

The COVID -19 infections is rapidly spreading throughout the world, and the lack of medical cure is seen as the most serious problem. According to the study's results revealing FVP is not superior to other antivirals, patients who received Favipiravir presented with more severe symptoms, more comorbidities, more complications, and is not effective in controlling the cytokine storm which negatively impact the efficacy of Favipiravir.

FVP therapy had no influence on ICU and hospital length of stay in comparison with the control group as well as in the overall mortality rate among the FVP group was not statistically significant.

Although our study with FVP did not show any promising benefit among COVID-19 patients, there is a lot of upside for this antiviral. In short, further research is needed to understand how FVP along with other treatments can improve the length of stay among COVID-19 patients admitted to the ICU.

Limitations

This study collected data from 5 tertiary hospitals in Riyadh, but has some limitations include relatively small sample size and retrospective nature of the study is not possible to rule out all confounders.

Strengths

This study has several strengths. First, the data being collected from multicenter tertiary hospitals using a, MOH electronic health record of patients with COVID-19 associated critical illness reported in the Saudi Arabia. Second, our findings mirror the ongoing outbreak of COVID-19 in Saudi Arabia, in addition, the study includes a comparator arm (control group), and lastly data analyses were done with near-complete data.

Acknowledgments

The authors would like to thank all the ICU doctors, and nurses, who fought against COVID-19 and supported this research

References

[1] M. Gavriatopoulou *et al.*, "Emerging treatment strategies for COVID-19 infection," (in eng), *Clinical and experimental medicine,* vol. 21, no. 2, pp. 167-179, 2021, doi: 10.1007/s10238-020-00671-y.

[2] T. Koritala *et al.*, "A narrative review of emergency use authorization versus full FDA approval and its effect on COVID-19 vaccination hesitancy."

[3] W. C. Ko *et al.*, "Arguments in favour of remdesivir for treating SARS-CoV-2 infections," (in eng), *Int J Antimicrob Agents,* vol. 55, no. 4, p. 105933, Apr 2020, doi: 10.1016/j.ijantimicag.2020.105933.

[4] "World Health Organization Coronavirus disease (COVID-19) weekly epidemiological update and weekly operational update." https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed.

[5] E. Prompetchara, C. Ketloy, and T. Palaga, "Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic," (in eng), *Asian Pac J Allergy Immunol,* vol. 38, no. 1, pp. 1-9, Mar 2020, doi: 10.12932/ap-200220-0772.

[6] Y. M. Alsofayan, S. M. Althunayyan, A. A. Khan, A. M. Hakawi, and A. M. Assiri, "Clinical characteristics of COVID-19 in Saudi Arabia: A national retrospective study," (in eng), *Journal of infection and public health,* vol. 13, no. 7, pp. 920-925, 2020, doi: 10.1016/j.jiph.2020.05.026.

[7] Z. Wu and J. M. McGoogan, "Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention," (in eng), *Jama,* vol. 323, no. 13, pp. 1239-1242, Apr 7 2020, doi: 10.1001/jama.2020.2648.

[8] W. J. Guan *et al.*, "Clinical Characteristics of Coronavirus Disease 2019 in China," (in eng), *N Engl J Med,* vol. 382, no. 18, pp. 1708-1720, Apr 30 2020, doi: 10.1056/NEJMoa2002032.

[9] D. Wang *et al.*, "Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China," (in eng), *Jama,* vol. 323, no. 11, pp. 1061-1069, Mar 17 2020, doi: 10.1001/jama.2020.1585.

[10] P. Goyal *et al.*, "Clinical Characteristics of Covid-19 in New York City," in *N Engl J Med*, vol. 382, no. 24), 2020, pp. 2372-2374.

[11] B. Cao *et al.*, "A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19," (in eng), *N Engl J Med,* vol. 382, no. 19, pp. 1787-1799, May 7 2020, doi: 10.1056/NEJMoa2001282.

[12] M. Bartoletti *et al.*, "Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: a multicentre study," (in eng), *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases,* vol. 27, no. 1, pp. 105-111, 2021, doi: 10.1016/j.cmi.2020.09.014.

[13] P. Horby *et al.*, "Dexamethasone in Hospitalized Patients with Covid-19," (in eng), *N Engl J Med,* vol. 384, no. 8, pp. 693-704, Feb 25 2021, doi: 10.1056/NEJMoa2021436.

[14] M. Mahévas *et al.*, "Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data," *Bmj,* vol. 369, 2020.

[15] N. Sinha and G. Balayla, "Hydroxychloroquine and COVID-19," *Postgraduate Medical Journal,* vol. 96, no. 1139, p. 550, 2020, doi: 10.1136/postgradmedj-2020-137785.

[16] T. Fiolet, A. Guihur, M. E. Rebeaud, M. Mulot, N. Peiffer-Smadja, and Y. Mahamat-Saleh, "Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis," (in eng), *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases,* vol. 27, no. 1, pp. 19-27, 2021, doi: 10.1016/j.cmi.2020.08.022.

[17] J. Liu *et al.*, "Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro," (in eng), *Cell Discov,* vol. 6, p. 16, 2020, doi: 10.1038/s41421-020-0156-0.

[18] J. H. Beigel *et al.*, "Remdesivir for the Treatment of Covid-19 - Final Report," (in eng), *The New England journal of medicine,* vol. 383, no. 19, pp. 1813-1826, 2020, doi: 10.1056/NEJMoa2007764.

[19] C. Liang *et al.*, "A promising antiviral candidate drug for the COVID-19 pandemic: A mini-review of remdesivir," (in eng), *European journal of medicinal chemistry,* vol. 201, pp. 112527-112527, 2020, doi: 10.1016/j.ejmech.2020.112527.

[20] A. L. Totura and S. Bavari, "Broad-spectrum coronavirus antiviral drug discovery," (in eng), *Expert opinion on drug discovery,* vol. 14, no. 4, pp. 397-412, 2019, doi: 10.1080/17460441.2019.1581171.

[21] S. Perazzolo, L. Zhu, W. Lin, A. Nguyen, and R. J. Y. Ho, "Systems and Clinical Pharmacology of COVID-19 Therapeutic Candidates: A Clinical and Translational Medicine Perspective," (in eng), *J Pharm Sci,* vol. 110, no. 3, pp. 1002-1017, Mar 2021, doi: 10.1016/j.xphs.2020.11.019.

[22] C. M. Chu *et al.*, "Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings," (in eng), *Thorax,* vol. 59, no. 3, pp. 252-6, Mar 2004, doi: 10.1136/thorax.2003.012658.

[23] K. T. Choy *et al.*, "Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro," (in eng), *Antiviral Res,* vol. 178, p. 104786, Jun 2020, doi: 10.1016/j.antiviral.2020.104786.

[24] L. Oestereich, A. Lüdtke, S. Wurr, T. Rieger, C. Muñoz-Fontela, and S. Günther, "Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model," (in eng), *Antiviral Res,* vol. 105, pp. 17-21, May 2014, doi: 10.1016/j.antiviral.2014.02.014.

[25] C. Q. Bai *et al.*, "Clinical and Virological Characteristics of Ebola Virus Disease Patients Treated With Favipiravir (T-705)-Sierra Leone, 2014," (in eng), *Clin Infect Dis,* vol. 63, no. 10, pp. 1288-1294, Nov 15 2016, doi: 10.1093/cid/ciw571.

[26] L. Delang, R. Abdelnabi, and J. Neyts, "Favipiravir as a potential countermeasure against neglected and emerging RNA viruses," (in eng), *Antiviral Res,* vol. 153, pp. 85-94, May 2018, doi: 10.1016/j.antiviral.2018.03.003.

[27] M. Bosaeed *et al.*, "Multicentre randomised double-blinded placebo-controlled trial of favipiravir in adults with mild COVID-19," (in eng), *BMJ Open,* vol. 11, no. 4, p. e047495, Apr 14 2021, doi: 10.1136/bmjopen-2020-047495.

[28] Y. Furuta, T. Komeno, and T. Nakamura, "Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase," (in eng), *Proceedings of the Japan Academy. Series B, Physical and biological sciences,* vol. 93, no. 7, pp. 449-463, 2017, doi: 10.2183/pjab.93.027.

[29] Z. Almoosa *et al.*, "Favipiravir versus standard of care in patients with severe COVID-19 infections: A retrospective comparative study," (in eng), *J Infect Public Health,* vol. 14, no. 9, pp. 1247-1253, Aug 24 2021, doi: 10.1016/j.jiph.2021.08.022.

[30] Q. Cai *et al.*, "Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study," *Engineering,* vol. 6, no. 10, pp. 1192-1198, 2020/10/01/ 2020, doi: https://doi.org/10.1016/j.eng.2020.03.007.

[31] "The Kingdom of Saudi Arabia's experience in health preparedness and response to COVID-19 pandemic. ." Riyadh: Government of Saudi Arabia; 2020. https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Documents/COVID-19-NATIONAL.pdf (accessed accessed 6 December 2020).).

[32] "Saudi Arabia physicians total number 2010–2019 [Internet]. ." Hamburg: Statista; 2021. https://www.statista.com/statistics/608539/total-number-of-physicians-in-saudi-arabia (accessed accessed 1 March 2021)).

[33] "Coronavirus disease 19 guidelines. Riyadh: Ministry of Health, Saudi Arabia; 2020." Ministry of Health, Saudi Arabia; 2020. https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/covid19.aspx (accessed 31 December 2020).

[34] A. Khorram-Manesh, K. Goniewicz, A. Hertelendy, and M. Dulebenets, *Handbook of Disaster and Emergency Management (2nd Edition, 2021)*. 2021.

[35] A. Al-Wathinani *et al.*, "Increased Emergency Calls during the COVID-19 Pandemic in Saudi Arabia: A National Retrospective Study," *Healthcare,* vol. 9, no. 1, 2021, doi: 10.3390/healthcare9010014.

[36] A. Alharthy *et al.*, "Clinical Characteristics and Predictors of 28-Day Mortality in 352 Critically Ill Patients with COVID-19: A Retrospective Study," (in eng), *Journal of epidemiology and global health,* vol. 11, no. 1, pp. 98-104, 2021, doi: 10.2991/jegh.k.200928.001.

[37] M. J. Cummings *et al.*, "Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study," (in eng), *Lancet (London, England),* vol. 395, no. 10239, pp. 1763-1770, 2020, doi: 10.1016/S0140-6736(20)31189-2.

[38] M. G. Argenziano *et al.*, "Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series," (in eng), *Bmj,* vol. 369, p. m1996, May 29 2020, doi: 10.1136/bmj.m1996.

[39] J. Lighter *et al.*, "Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission," in *Clin Infect Dis*, vol. 71, no. 15), 2020, pp. 896-897.

[40] Y. Wang, Y. Zhou, Z. Yang, D. Xia, Y. Hu, and S. Geng, "Clinical Characteristics of Patients with Severe Pneumonia Caused by the SARS-CoV-2 in Wuhan, China," (in eng), *Respiration;*

international review of thoracic diseases, vol. 99, no. 8, pp. 649-657, 2020, doi: 10.1159/000507940.

[41] S. Xiong *et al.*, "Clinical characteristics of 116 hospitalized patients with COVID-19 in Wuhan, China: a single-centered, retrospective, observational study," (in eng), *BMC infectious diseases,* vol. 20, no. 1, pp. 787-787, 2020, doi: 10.1186/s12879-020-05452-2.

[42] X. Yang *et al.*, "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study," (in eng), *Lancet Respir Med,* vol. 8, no. 5, pp. 475-481, May 2020, doi: 10.1016/s2213-2600(20)30079-5.

[43] C. Chen *et al.*, "Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial," *medRxiv,* p. 2020.03.17.20037432, 2020, doi: 10.1101/2020.03.17.20037432.

[44] F. Zhou *et al.*, "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study," (in eng), *Lancet,* vol. 395, no. 10229, pp. 1054-1062, Mar 28 2020, doi: 10.1016/s0140-6736(20)30566-3.

[45] L. Hu *et al.*, "Risk Factors Associated With Clinical Outcomes in 323 Coronavirus Disease 2019 (COVID-19) Hospitalized Patients in Wuhan, China," (in eng), *Clin Infect Dis,* vol. 71, no. 16, pp. 2089-2098, Nov 19 2020, doi: 10.1093/cid/ciaa539.

[46] C. Qin *et al.*, "Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China," (in eng), *Clin Infect Dis,* vol. 71, no. 15, pp. 762-768, Jul 28 2020, doi: 10.1093/cid/ciaa248.

[47] Q. Ye, B. Wang, and J. Mao, "The pathogenesis and treatment of the `Cytokine Storm' in COVID-19," (in eng), *J Infect,* vol. 80, no. 6, pp. 607-613, Jun 2020, doi: 10.1016/j.jinf.2020.03.037.

[48] I. Huang, R. Pranata, M. A. Lim, A. Oehadian, and B. Alisjahbana, "C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis," (in eng), *Therapeutic advances in respiratory disease,* vol. 14, pp. 1753466620937175-1753466620937175, Jan-Dec 2020, doi: 10.1177/1753466620937175.

[49] B. Yu *et al.*, "Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis," (in eng), *J Thromb Thrombolysis,* vol. 50, no. 3, pp. 548-557, Oct 2020, doi: 10.1007/s11239-020-02171-y.

[50] S. Vidali *et al.*, "D-dimer as an indicator of prognosis in SARS-CoV-2 infection: a systematic review," (in eng), *ERJ Open Res,* vol. 6, no. 2, Apr 2020, doi: 10.1183/23120541.00260-2020.

[51] C. Wu *et al.*, "Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China," (in eng), *JAMA Intern Med,* vol. 180, no. 7, pp. 934-943, Jul 1 2020, doi: 10.1001/jamainternmed.2020.0994.

[52] S. F. van Eeden and J. C. Hogg, "Immune-Modulation in Chronic Obstructive Pulmonary Disease: Current Concepts and Future Strategies," (in eng), *Respiration,* vol. 99, no. 7, pp. 550-565, 2020, doi: 10.1159/000502261.

[53] Y. Liu *et al.*, "Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury," (in eng), *Sci China Life Sci,* vol. 63, no. 3, pp. 364-374, Mar 2020, doi: 10.1007/s11427-020-1643-8.

[54] E. Mortaz *et al.*, "Serum cytokine levels of COVID-19 patients after 7 days of treatment with Favipiravir or Kaletra," (in eng), *International immunopharmacology,* vol. 93, pp. 107407-107407, 2021, doi: 10.1016/j.intimp.2021.107407.

[55] C. Wang *et al.*, "Cytokine Levels in the Body Fluids of a Patient With COVID-19 and Acute Respiratory Distress Syndrome: A Case Report," (in eng), *Annals of internal medicine,* vol. 173, no. 6, pp. 499-501, 2020, doi: 10.7326/L20-0354.

[56] M. Solaymani-Dodaran *et al.*, "Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia," (in eng), *International immunopharmacology,* vol. 95, pp. 107522-107522, 2021, doi: 10.1016/j.intimp.2021.107522.

[57] H. Kocayiğit *et al.*, "Observational study of the effects of Favipiravir vs Lopinavir/Ritonavir on clinical outcomes in critically Ill patients with COVID-19," *Journal of Clinical Pharmacy and Therapeutics,* vol. 46, no. 2, pp. 454-459, 2021.

[58] F. Khamis *et al.*, "Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia," (in eng), *Int J Infect Dis,* vol. 102, pp. 538-543, Jan 2021, doi: 10.1016/j.ijid.2020.11.008.

[59] P.-J. Chen, C.-M. Chao, and C.-C. Lai, "Clinical efficacy and safety of favipiravir in the treatment of COVID-19 patients," (in eng), *The Journal of infection,* vol. 82, no. 5, pp. 186-230, 2021, doi: 10.1016/j.jinf.2020.12.005.

[60] D. B. Shrestha, P. Budhathoki, S. Khadka, P. B. Shah, N. Pokharel, and P. Rashmi, "Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis," (in eng), *Virol J,* vol. 17, no. 1, p. 141, Sep 24 2020, doi: 10.1186/s12985-020-01412-z.

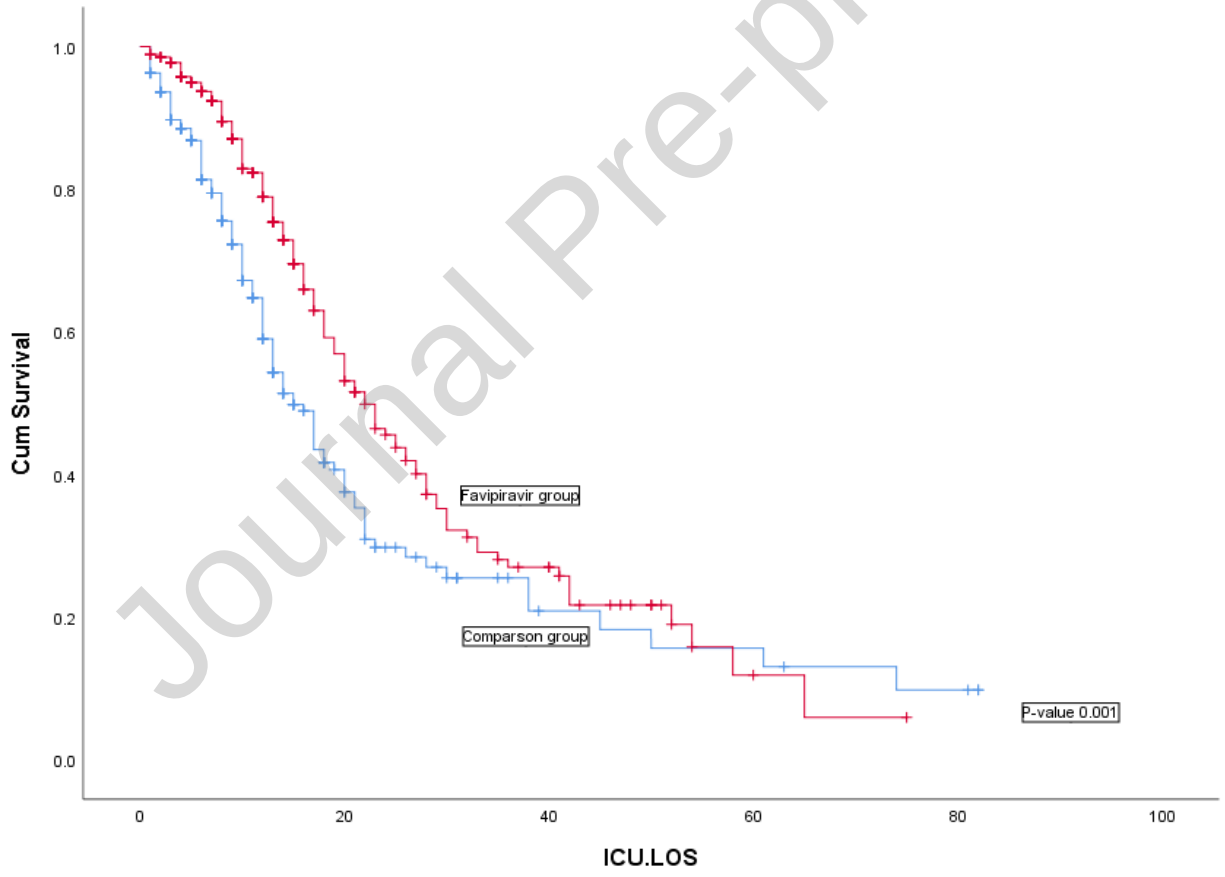

Figure 1: Kaplan meier curve survival of critically ill patients with COVID – 19 pneumonia

Table I: Baseline characteristics (n = 538).

Characteristics	**Received Favipiravir N= 269 (50.0%)**	**Didn't receive Favipiravir N=269 (50.0%)**	***P-value***
Hospitals			
Hospital A	168 (62.5%)	079 (29.4%)	
Hospital B	060 (22.3%)	133 (49.5%)	0.0001
Hospital C	026 (09.7%)	035 (13.0%)	
Hospital D	013 (04.8%)	013 (04.8%)	
Hospital E	002 (00.7%)	009 (03.3%)	
Nationality			
Saudi	201 (74.7%)	120 (44.6%)	0.0001
Non-Saudi	068 (25.3%)	149 (55.4%)	
Gender			
Males	177 (65.8%)	198 (73.6%)	0.049
Female	092 (34.2%)	71 (26.4%)	
Smoker			
Yes	033 (12.3%)	036 (13.4%)	0.69
No	236 (87.7%)	233 (86.6%)	
Age	57.23 ± 15.16 years	57.65 ± 12.35 years	0.72
BMI	31.61 ± 7.33	30.93 ± 4.95	0.21

Table II: Presenting signs and comorbidities (n = 538).

Symptoms and laboratory findings	**Received Favipiravir N = 269(50.0%)**	**Didn't receive Favipiravir N=269 (50.0%)**	***p-value***
Signs and Symptoms of presentation	231 (85.9%)	228 (84.8%)	0.715
SOB	013 (04.8%)	009 (03.3%)	0.384
Rhinorrhea	181 (67.3%)	191 (71.0%)	0.351
Fever	020 (07.4%)	014 (05.2%)	0.288
Abdominal pain	162 (60.2%)	171 (64.3%)	0.016
Cough	045 (16.7%)	026 (09.7%)	0.328
Chest pain	053 (19.7%)	019 (07.1%)	0.001
Headache	047 (17.5%)	0.13 (04.8%)	0.001
Joint pain	054 (20.1%)	022 (08.2%)	0.001
Muscle ache	067 (24.9	039 (14.5%)	0.002

Fatigue	%)	019 (07.1%)	0.001
Sore throat	051 (19.0%)		
Comorbidities			
Diabetes mellitus (DM)	179 (66.5%)	152 (56.5%)	0.017
Hypertension (HTN)	152 (56.5%)	139 (51.7%)	0.143
Ischemic heart disease	040 (14.9%)	032 (11.9%)	0.194
(IHD)	019 (07.1%)	010 (03.7%)	0.110
Heart failure (HF)	039 (14.5%)	021 (07.8%)	0.012
Bronchial asthma (BA)	027 (05.0%)	016 (03.0%)	0.026
Chronic kidney disease			
(CKD)			

Table III-A: Laboratory findings between the two groups (n = 538).

Laboratory findings	**Received Favipiravir n= 269(50.0%)**	**Didn't receive Favipiravir n=269 (50.0%)**	***P - value***
Leukocytes	8.87 ± 4.88	9.97 ± 5.59	0.020
Erythrocyte	52.86 ± 32.69	56.80 ± 47.55	0.464
sedimentation rate (ESR)			
D-Dimer	2.97 ± 5.70	5.21 ± 9.59	*0.011*
Ferritin	932.52 ± 1260.64	1123.19 ± 2098.46	0.352
C reactive protein (CRP)	106.03 ± 85.58	170.55 ± 282.69	*0.016*
Hemoglobin	11.87 ± 2.15	12.50 ± 7.14	0.170
Lactic acid	518.99 ± 509.79	614.90 ± 606.73	0.113
dehydrogenase (LDH)			
Alanine	56.63 ± 102.36	62.83 ± 109.79	0.539
aminotransferase (ALT)			
Aspartate	74.64 ± 134.93	103.41 ± 160.73	0.153
aminotransferase (AST)			
Creatinine	130.6 ± 160.86	140.61 ± 149.93	0.475

Table III B: Supplemental therapies between the two groups (n = 538).

Supplemental therapy	**Received Favipiravir n=269(50.0%)**	**Didn't receive Favipiravir n=269 (50.0%)**	***P - value***
Corticosteroids	227 (84.4%)	153 (56.9%)	***0.001***
Tocilizumab	151 (56.1%)	050 (18.6%)	***0.001***
Remdesivir	002 (0.07%)	001 (0.04%)	0.467

Chloroquine	020 (7.4%)	068 (25.3%)	***0.001***
Azithromycin	164 (61.0%)	172 (63.9%)	0.448

Table IV: Intervention and overall clinical outcome (n = 538).

Characteristics	**Received Favipiravir 269(50.0%)**	**Didn't receive Favipiravir 269 (50.0%)**	***P-value***
Length of hospital stay	24.98 ± 20.76 days MDN 18.00 days IQR 17	18.29 ± 19.14 days MDN 14.00 days IQR14	0.001
Length of ICU stay	16.31 ± 14.09 days MDN 12.5 days, IQR 14	12.20 ± 13.56 days MDN 9.00 days, IQR 9	0.001
ARDS			
Severe ARDS	076 (28.3%)	070 (26.9%)	0.270
Mild and no ARDS	193 (71.7%)	199 (73.1%)	
Overall survival			
Death	119 (44.2%)	128 (47.6%)	0.440
Alive	150 (55.8%)	141 (52.4%)	